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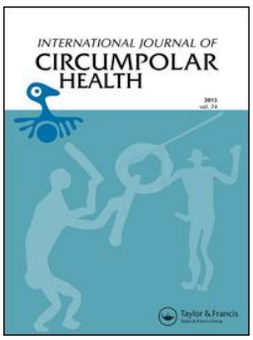

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Improved survival of head and neck cancer patients in Greenland

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ABSTRACT

Previously, head and neck cancer (HNC) patients in Greenland have had significant diagnostic delay and poor survival rates. From 2005-2009 several initiatives have been made to ensure faster diagnosis and better survival. The aim of this study was to compare the prognosis before and after these initiatives were introduced.

All Greenlandic patients diagnosed with HNC between 2005 and 2012 were included. Data were retrieved from medical records and national databases and compared with the period 1994-2003.

A total of 98 patients were identified. Diagnostic delay was significantly lower compared to the period 1994–2004 (p=0.048). The 3-year overall survival was 56% for all HNC and 47% for nasopharyngeal carcinomas. We found that patients with HNC between 1994 and 2003 had a higher risk of death from all reasons compared with the period 2005–2012 (HR 2.17; CI 1.46–3.23) after adjustments for stage and diagnostic delay.

Patients with head HNC in Greenland from 2005-2012 were diagnosed earlier and had a better overall survival compared to the period 1994–2003. The change in survival is more likely to be due to improvement in treatment rather than the initiated interventions. Although survival has improved in Greenland, demographic problems and lack of specialists remain a challenge.

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Head and neck cancer; Inuit; survival; delay

Introduction

Head and neck cancer is frequent in the Inuit population who primarily inhabit the circumpolar region with the majority living in Greenland, Canada and Alaska [1]. Among the Inuit there is a high incidence of cancer of the nasopharynx and salivary glands compared to their respective national populations in Denmark, Canada and the United States [2].

The majority of the nasopharyngeal carcinomas (NPC) in the Inuit population is the undifferentiated type and infection with Epstein–Barr virus is believed to be one of the most important aetiological factors [3]. Furthermore, studies have found an increased risk of NPC and salivary gland cancer among first degree-relatives and in family clusters supporting the existence of a hereditary component [4].

Head and neck cancer is primarily a locoregional disease and is therefore potentially curable with either surgery or radiotherapy/chemo-radiotherapy or a combination of both. It often metastasises regionally while distant metastases are rare and typically seen in late stage disease [5]. Early diagnosis of head and neck cancer is important as it has been shown that diagnostic delay increases risk of mortality [6]. Furthermore, it is known that head and neck cancer proliferate rapidly and that delay in treatment initiation can result in stage progression [7,8] and have a negative effect on survival [9]. This emphasises the importance of reducing diagnostic delay and treatment delay to ensure better prognosis for patients with head and neck cancer.

Head and neck cancer arises in anatomically and functionally complex areas. Impairment of these areas from both treatment and disease can cause pain and can damage essential functions as breathing, speech, eating and sense of smell/taste which can have a profound negative effect on physical, emotional and social functioning [10]. Follow-up on head and neck cancer patients is essential to identify locoregional recurrence or metastasis and to assess treatment consequences and restore nutritional and psychosocial status [11]

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Close and structured follow-up on these patients of ear, nose and throat (ENT) specialists or oncologists is a challenge in Greenland due to the demographic structure with scattered communities far from the regional health centres and the difficulty in recruiting specialists [12].

Jensen et al. investigated treatment response and survival of head and neck cancer in the Greenland Inuit population between 1994 and 2003 [13]. They found significant delay in the diagnosis and treatment of head and neck cancer. Furthermore, they found late disease stage at diagnosis and corresponding poor survival rates irrespectively of disease site. Since that study several initiatives have been made to ensure faster diagnosis and better survival for patients with head and neck cancer in Greenland. In early 2005 an ENT specialist was based permanently in the capital Nuuk in Greenland to refer, diagnose and perform follow-up care for head and neck cancer patients. Previously this was done by the primary sector or by ENT specialists from Denmark visiting the remote areas once a year. Additionally, a head and neck cancer awareness campaign was aired on national television in autumn 2009. At the same time healthcare professionals at Dronning Ingrid's Hospital, Nuuk and several other health care districts in Greenland were educated in how to manage head and neck cancer patients after treatment. In order to investigate the impact of these initiatives, we performed a new analysis of all head and neck cancer patients in Greenland diagnosed 2005–2012 in order to describe treatment delay, diagnostic delay and prognosis compared with the period 1994–2003.

Materials and methods

This is a retrospective study including all patients resident in Greenland diagnosed with head and neck cancer between 1 June 2005 and 31 December 2012, and these data was compared with data for the time period 1 January 1994 to 31 December 2003.

Data for the earlier period has been described previously [13], so we give a summary here. The Danish civil registration system, the Danish Cancer registry and hospital-based registries were used to identity all patients resident in Greenland diagnosed with head and neck cancer. A total of 125 inuit patients were identified. Date of first symptom, confirmed histological diagnosis and first day of treatment were obtained from medical records. Information on death was obtained from patient files and the medical public health officer in Greenland. All surviving patients were observed for at least 4 years.

Data for the latest period as well as comparison of the two periods will be described in the following section. All individuals in Greenland are registered in the Danish Civil Registration system [14] and have a civil registration number (CRS). Patients with a Greenlandic CRS number combined with an ICD-10 code for carcinoma in the pharynx, larynx, oral cavity, nasal cavity and sinuses, salivary gland and thyroid gland were included. Patients with cervical lymph node metastases but an unknown primary tumour were included because over 90% of these represent malignancies within Waldeyer's ring in the pharynx [15]. The diagnoses were validated using the Danish Pathology Registry. Clinical information was obtained from medical records from Rigshospitalet in Copenhagen, Denmark, and from Dronning Ingrid's Hospital in Nuuk, Greenland. Tumours were staged prospectively according to the Union for International Cancer Control (UICC) version 7.

Time course

Dates for the following events were registered: first symptom, confirmed histological diagnosis, first day of treatment and death. Age was estimated at the time of histological diagnosis. Diagnostic delay was calculated from date of first symptom to date of histological diagnosis. The time from verified histological diagnosis to first day of treatment was calculated as treatment delay and finally the overall delay was calculated from date of first symptom to first day of treatment. Information on death was extracted from the journals last updated 18 October 2015.

Statistical analysis

Incidence rates were age-standardised according to the 2000 world standard population.

The Mann–Whitney U test was used to assess differences between groups of continuous variables. The relationship between two categorical variables was calculated using chi-square test.

We estimated overall survival rates using the Kaplan–Meier model. Overall survival was defined as the time from the initial diagnosis to date of death. Patients were followed until death or the follow-up cut-off date 18 October 2015. Censoring was made if patients were alive at the follow-up cut-off date. Univariate comparison of survival was performed using the log-rank test. The variables age, gender, localisation, stage, diagnostic delay and period were entered into a multivariate analysis using a Cox proportional hazards model with backward elimination. All results are given as two-sided

values. All statistical analyses were performed using IBM SPSS statistics version 22.0.0.

Results

The 98 patients diagnosed with head and neck cancer in Greenland between 2005 and 2012 comprised 39 females and 59 men with an age range of 5–81 years and a median age of 57 years (one patient aged 5 years had an embryonal rhabdomyosarcoma). The age-standardised incidence rate for all head and neck cancers was 25/100,000 persons-years for males and 19/100,000 persons-years for females. The incidence rate of NPC was 9/100,000 persons-years for males and 4/100,000 persons-years for females. The incidence of laryngeal carcinomas was low with rates of 2/100,000 persons-years for males and <1/100,000 persons-years for females (Table 1). The most common tumour localisation was the nasopharynx with almost one-third of all cases.

According to UICC TNM classification, we found that 14 (14%) were stage I–II, 62 (63%) were stage III–IV and 22 (22%) were of unknown stage (Table 2). For the largest group, NPC, the majority of patients (87%) were diagnosed in stage III–IV.

The median delay from first symptom to histological diagnosis (diagnostic delay) for all patients was 168 days with a significant difference (p=0.02) between the two genders with females having a larger median diagnostic delay than men (218 days vs. 139 days).

Three patients did not receive any treatment, one refused treatment, one could not receive treatment due to severe morbidity and no data was available on why the last patient did not receive treatment.

In Table 3 the collected data from the period 2005–2012 has been compared with the prior study period (1994–2003) using univariate statistics. In the comparison, stage was divided into two groups, stage I–II and stage III–IV. We found no significant differences between the two populations regarding the distribution in incidence, age, gender, localisation or stage. We found that diagnostic delay was significantly lower in the latest period compared to the period 1994–2004 (p=0.048). For all head and neck cancer patients we found a 3-year overall survival of 56% compared with 39% in the prior period (Figure 1). The 3-year overall survival for NPC was 47% and for oral and oropharyngeal carcinomas it was 46% and 43%, respectively. When we compared overall survival for all head and neck cancers using the log-rank test we found a significant difference between the two population groups (p=0.04). The greatest difference in overall survival was found for NPC (p=0.026) but also oral -and oropharyngeal carcinomas had a better overall survival in this study period compared to 1994–2003 although this difference was not significant.

To examine whether the significant improvement in overall survival in the present study compared to the latter could be explained by differences in the variables collected, we performed a multivariate analysis. We found that patients with head and neck cancer from Greenland between 1994 and 2003 had a significant increased risk of death from all reasons with a hazard ratio of 2,17 (CI 1.46–3.23) compared with the period 2005–2012 after adjusting for age, gender, localisation, stage and diagnostic delay (Table 4).

Table 1. Numbers and incidence of head and neck cancer per 100,000 persons-years in Greenland in the period 2005–2012.

	Males (n)	Age mean	Crude rate	As[a] rate	Females (n)	Age mean	Crude rate	As[a] rate
Nasopharynx	22	59	10	9	8	56	4	4
Oropharynx	10	60	5	4	4	59	2	2
Hypopharynx	6	62	3	3	0			
Larynx	6	58	3	2	1	52	< 1	< 1
Salivary gland	5	39	2	2	5	53	3	2
Oral cavity	6	62	3	3	7	63	4	3
Thyroid	1	50	< 1	< 1	12	47	6	6
Others	3	68	1	1	2	36	1	1
All cancers	59	58	26	25	39	53	20	19

[a]Age-standardised using the 2000 world standard population.

Table 2. Stage according to UICC 1997 in Greenlandic head and neck cancer patients.

	2005–2012				1994–2003			
	n	Stage I–II %	Stage III–IV %	Stage unknown %	n	Stage I–II %	Stage III–IV %	Stage unknown %
Oral cavity	14	36	36	29	25	20	68	12
Nasopharynx	30	7	87	7	42	10	88	2
Oropharynx	14	0	81	19	13	23	69	8
Salivary gland	10	30	60	10	13	54	39	8
All head and neck cancers	98	14	63	22	125	24	69	7

Table 3. Comparison of all head and neck cancer patients in Greenland between the period 1994–2003 and 2005–2012.

Variables	1994–2003	2005–2012	p-Value
As[a] rate females (cases per 100,000 persons-years)	19	20	
As[a] rate males (cases per 100,000 persons-years)	28	26	
Age (median)	58	57.5	0.923
Gender (n (%))			0.975
Female	50 (40%)	39 (40%)	
Male	75 (60%)	59 (60%)	
Time course (median days)			
Diagnostic delay	207	168	0.048
Treatment delay	40	32	0.272
Overall delay	249	201	0.051
Localisation (n (%))			0.539
Nasopharynx	42 (34%)	30 (31%)	
Oropharynx	13 (10%)	14 (14%)	
Hypopharynx	6 (5%)	6 (6%)	
Larynx	10 (8%)	7 (7%)	
Salivary gland	13 (10%)	10 (10%)	
Oral cavity	27 (22%)	13 (13%)	
Thyroid	12 (10%)	13 (13%)	
Other	2 (2%) (a)	5 (5%) (b)	
Stage (n (%))			0.114
Stage I–II	33 (26%)	14 (14%)	
Stage III–IV	83 (66%)	62 (63%)	
Unknown stage	9 (7%)	22 (22%)	
Overall survival (3-years OS)	39%	56%	0.04
Total (n)	125	98	

[a] Age-standardised using the 2000 world standard population.
[b] Unknown primary.
[c] Three sinonasal, one embryonal rhabdomyosarcoma and one unknown primary.

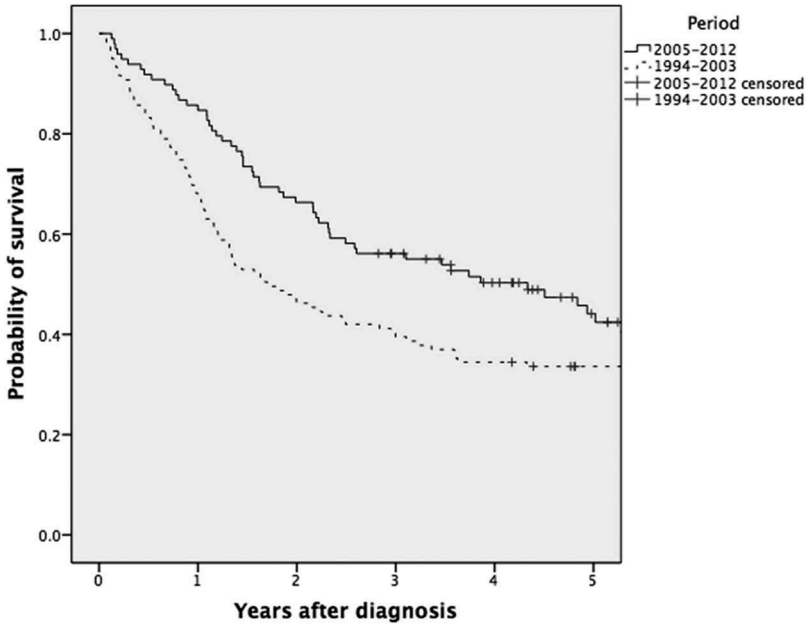

Figure 1. Overall survival in Greenland for all head and neck cancer patients.

Discussion

In this study, we have retrospectively investigated all head and neck cancer patients in the largest Inuit population in the world over a period of 7.5 years and compared the time course and prognosis of these patients with the period 1994–2003. In multivariate analysis, we found a significant better overall survival for all head and neck cancer patients in Greenland compared with the period 1994–2003. The most significant improvement in overall survival was seen for NPC patients where the 3-year overall survival increased from 23% to 47%.

Furthermore, we found a significant shorter diagnostic delay in this study compared to the period 1994–2003.

The disease stage at diagnosis seems to be largely unchanged for NPC between the two periods with

Table 4. Multivariate analysis with hazard ratios for death among all head and neck cancer patients in Greenland from the periods 1994–2003 and 2005–2012.

Covariate	HR	p-Value	95% CI
Age	1.06	**<0.001**	1.05–1.08
Gender	0.85	0.41	0.58–1.25
Localisation	0.95	0.22	0.87–1.03
Stage	1.87	**<0.001**	1.49–2.35
Diagnostic delay	1	0.89	0.99–1.00
Period	2.18	**<0.001**	1.46–3.23

the greatest part of NPC patients diagnosed in the more advanced stages. However, even at the same stage there may be large variations in tumour size. As for the other tumour localisations, it is not possible to describe trends in stage between the periods due to the lower number of patients and a larger proportion of cases with unknown stage.

Patients with NPC in the United States and Denmark have also achieved improvement in survival over the last decades. Jia-Wei et al. analysed data from the Surveillance Epidemiology and End Results programme and found an increase in 5-year overall survival from 46.6 % between 1990 and 1999 to 54.7% between 2000 and 2007 [16]. The same development was seen in Denmark where the 3-year overall survival for NPC was 72% in a Danish study from 2008 [17] which is significantly better than previous studies [18]. One of the main reasons for the increase in survival rates for NPC patients was the introduction of concomitant chemo-radiotherapy and the use of intensity-modulated radiotherapy. In 1998 Al-Sarraf et al. found improvement in survival for patients with advanced NPC receiving chemo-radiotherapy compared to radiotherapy alone [19] and later this was verified in a Cochrane review [20]. Although the overall survival in Greenland has improved significantly, it is still not comparable to Denmark or the United States. Other factors that could explain the improvement in survival are the small reduction in the use of tobacco and alcohol over the past two decades [21,22] as well as the more organised follow-up procedures, use of CT and MRI scanning and more focus on rehabilitation including nutrition which was enrolled after an ENT specialist was permanently based in Nuuk, Greenland, from June 2005.

Comorbidity is common among head and neck cancer patients and is known to have a significant negative impact on outcome [23]. Advances in management of comorbidity or decreasing comorbidity burden over time might also have a positive influence on overall survival.

Until now human papilloma virus does not seem to play a dominant role in the development of oropharyngeal cancers in Greenland and cannot serve as explanation of the better survival in Greenland [24]. Furthermore, patients with head and neck cancer have probably been referred faster than before when the patients were diagnosed by non-specialists or ENT-specialists visiting once a year. This could explain the significant shorter diagnostic delay. Unfortunately, this change was not enough to diagnose patients in an earlier stage nor to have effect on survival (HR = 1 for diagnostic delay in Table 4).

Another explanation for the significant improvement in diagnostic delay could be the increased focus on head and neck cancer in Greenland with awareness campaigns on national television, which could have lead patients to the doctor earlier than before.

Our study naturally has some limitations. Firstly, diagnostic delay is subject to recall bias since it is based on retrospective, self-reported data on the time of first symptoms. However, recall bias would probably affect both periods equally, so the reduction in diagnostic delay between the two periods is probably not strongly affected by recall bias. Secondly, for the comparison of 3-year survival we haven't adjusted for treatment, despite this being probably the most important factor. Therefore, it is difficult to estimate the effect of intervention. Thirdly, as the Greenland population is small, there is a risk of coincidental changes in treatment delay, diagnostic delay and prognosis.

In summary, we found that patients with head and neck cancer in Greenland between 2005 and 2012 were diagnosed earlier and had a better overall survival compared to the period 1994–2003. Although survival has improved in Greenland, demographic problems and lack of specialists remain a challenge. The interval between first symptom and diagnosis is still very long, and the majority of patients are diagnosed in late stages.

Disclosure statement

No potential conflict of interest was reported by the authors.

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